REMARKS

Claims 34-48 are pending in the application. Claims 34, 35, 36, and 43 are currently amended.

CLAIM OBJECTIONS

An objection to the claims has been made by the Examiner. The Examiner has stated that Applicants must recite the chemical name for the notation VNP40101M followed by the notation in parentheses at the first occurrence of said notation. Applicants submit that claim 34 is currently amended to incorporate the required change.

CLAIM REJECTIONS

Rejection Under 35 U.S.C. §112, 1st Paragraph, Enablement

Claims 34-48 are rejected under 35 U.S.C. §112, 1st paragraph, for lack of enablement. The Examiner contends that the specification, while being enabling for a synergistic combination of VNP40101M with cytarabine (AraC) and fludarabine in the specific dosages recited in Table 2 (page 13) and Table 3 (page 14) of the specification, does not reasonably provide enablement for any other dose level of the combination of VNP40101M with cytarabine (AraC) and fludarabine that is outside the recited ranges in the specification to produce a synergism with respect to treating tumors.

Applicants respectfully submit that claims 34-36, and claim 43 have been amended to incorporate the specific doses listed in Table 2 and Table 3. Applicants also submit that the enablement rejection made against dependent claims 37-42, and

44-48 is also thereby obviated by amendment of claims 34-36, and claim 43. Accordingly, Applicants respectfully request that the rejection of claims 34-48 under 35 U.S.C. §112, 1st paragraph, be withdrawn.

Double Patenting, Nonstatutory Obviousness-Type

Claims 34-48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 70-73 of U.S. Patent No. 6,855,695 (the '695 patent). The Examiner states that the claims are not patentably distinct from each other because instant claims 34-35 are drawn to a composition comprising an amount of VPN 40101M in combination with cytarabine and fludarabine respectively, and that claims 36-48 are drawn to a method of treatment of tumors using the above composition. The Examiner recites Claims 70-73 of the '695 patent as being drawn to compositions and methods of treating tumors comprising substituted hydrazines and another antitumor agent including cytarabine. The Examiner also recites that Claims 70-73 of the '695 patent differ from the instant claims in that the instant claims employ only cytarabine and fludarabine as additional agents and also employ substituted aryl derivatives of VNP40101M. Applicants respectfully traverse this rejection.

Applicants submit that obviousness does not exist with respect to the present claims because the '695 patent does not teach or suggest doses for synergistic effect, one of the defining characteristics of the present invention, and one which has been written into the currently amended claims.

Claims 70-73 instead recite, in general fashion, the following:

70 - A method comprising administering to said patient an effective amount of a compound according to any of claims 1-22 in combination with at least one additional tumor agent.

Claim 71 recites a method comprising administering to the patient the enumerated compounds with selected anti-tumor agents, whereas claims 72 and 73 recite pharmaceutical compositions comprising an effective amount of the enumerated compounds with an additional anti-tumor agent, or a selected anti-tumor agent.

None of claims 71 through 73 recite dose limitations producing synergistic effects; nor do they, technically, recite the exact composition (VNP40101M) claimed in the present application. The specification of the '695 patent does not teach or suggest doses for synergistic effect. Since the '695 patent does not teach or suggest each and every aspect of the present invention, namely doses for synergistic effect, the '695 patent does not render the present invention obvious. Accordingly, Applicants respectfully request that the double patenting rejection of claims 34-48 be withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 34-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (International Journal of Toxicology, 2002, 21, 23-38) in view of Gourdeau et al. (U.S. 6,630,480). Applicants respectfully traverse this objection.

The Examiner has stated that Lee et al. teach that 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, also referred to herein as VNP40101M, is a novel

alklylating antitumor agent, shown to possess a broad spectrum of antitumor activity, but that Lee et al. does not suggest a combination of the compound with a nucleoside or a nucleoside analog or the use of the combination and another therapy for the treatment of tumors. Gourdeau et al. allegedly teaches the use of cytosine analogs and cytarabine for the treatment of leukemia and chronic myelogeous leukemias, as well as states that standard chemotherapy treatment includes treatment with two or more anticancer drugs, such as cytarabine and fludarabine.

The USPTO guidelines recite a non-exclusive list of examples of rationales which may be used to articulate a rejection based on obviousness, now at MPEP § 2143. These include:

(A) Combining prior art elements according to known methods to yield predictable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known technique to improve similar devices (methods, or products) in the same way;
(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Applicants submit that drug combinations of this type rarely yield "predictable results" or a "reasonable likelihood of success" due to the fact that, as noted by the Examiner on page 4 in the Office Action of December 3, 2008, "The instant claimed invention is highly *unpredictable*. It is… known in the art that synergistic or super additive effects for combinations of compounds in any amount are highly unpredictable. … Based on the teachings of the prior art it is highly unpredictable as to what dosages of the therapeutic agents will produce a synergistic combination for the treatment of tumors."

Applicants submit that there exist no teachings or suggestions in the cited references that specifically suggest a combination of compounds to produce a synergistic effect as claimed herein. Instead, the cited references only teach: 1) VNP40101M has activity as antitumor compound, 2) Gourdeau et al. says that chemotherapy involves treatment with more than one anticancer drug (column 1, lines 61-63, "Chemotherapy and leukemia usually involves a combination of two or more anti-cancer drugs"), and 3) the most important nucleosides that are used for the treatment of leukemia include cytarabine and fludarabine (as stated in US 6,630,480, column 2, lines 28-32: "Cytarabine, Fludarabine, Gemcitabine and Cladribine are some examples of nucleoside analogues which are currently important drugs in the treatment of leukemia"). Applicants submit that such teaching fails to account for the unpredictability in the art, and is

thereby reductivist. Applicants point to the fact that dosage experimentation was necessary, and that dosage limitations supporting synergistic effects have been introduced into the current claims. Moreover, Applicants submit that holding claims obvious under such an analysis would effectively create a situation in which any new combination of either VNP40101M or the "important nucleosides" with any other antitumor compound, would be obvious, regardless of unexpected results in doing so.

Applicants again reiterate the synergistic nature of the combinations presented in the current claims. Applicants also note that while courts have considered and rejected the notion that a new result or function or synergism is a requirement of patentability, such a "new and unexpected result or function or a so-called 'synergistic' effect" may support a holding of nonobviousness. American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, at 1360 (Fed. Cir. 1984).

In view of the above remarks, Applicants respectfully request that the rejection of claims 34-48 under 35 U.S.C. 103(a) be withdrawn.

Rejection Under 35 U.S.C. 103(a)

Claims 34-48 are rejected under 35 U.S.C. 103(a) as being obvious over Lin et al. (U.S. 6,855,695). Applicants respectfully traverse this rejection.

The Examiner has stated that because Lin et al. discloses closely related structural analogs of the parent compound disclosed in the present application (VNP40101M) and because, according to the Examiner, "Lin teaches that [the structural

analogs] can be administered with other conventional cancer therapies (col. 13, lines 32-34) and possible synergistic combinations" it would have been obvious to a person of ordinary skill in the art to search for combinations of the parent compound with cytarabine and fludarabine resulting in synergistic effects.

The Examiner has cited col. 14, lines 35-67 of Lin, et al. for the proposition that there may be unexpected synergism in these combinations. Within this cite, Lin et al. merely states, "In theory, the present compounds, which act by a mechanism to damage DNA, will act synergistically with compounds that act by a mechanism to reduce or prevent DNA repair." It also states, "In many instances, the co-administration of the present compounds with traditional anticancer agents produces a synergistic (i.e., more than additive) result which is unexpected." Lin, et al. does not provide any disclosure or guidance with respect to dosage ranges for such combinations of its claimed structural analogs with cytarabine or fludarabine. Given that the art is "highly unpredictable," as stated by the Examiner on p. 4 of the Office Action dated December 3, 2008, and that the Applicants were required to amend their present claims directed to combinations with VNP40101M to recite dosages in order to make them enabling, the present invention could not be obvious over a reference for analogues where there are no synergistic dose ranges taught or suggested.

Accordingly, Applicants respectfully request that the rejection of claims 34-48 under 35 U.S.C. 103(a) be withdrawn.

Conclusion

Applicants therefore believe that all grounds of objections and rejections raised in the outstanding Office Action have been fully addressed, and the claims are in condition for allowance. Accordingly, Applicants respectfully request favorable action to be rendered by the Examiner.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below. No fee is deemed necessary in connection with the filing of this response. However, if fees are required, authorization is given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Law Office of
Albert Wai-Kit Chan, PLLC
Attorney for Applicants
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, NY 11357
Tel:(718)799-1000
Fax:(718)357-8615
E-mail: chank@kitchanlaw.com